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(21) International Application Number: PCT/US93/02500 (22) International Filing Date: 16 March 1993 (16.03.93) (30) Priority data: 07/853,827 19 March 1992 (19.03.92) US (71) Applicant: ALLERGAN, INC. [US/US]; 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US). (72) Inventor: MEADOWS, David, Louis ; 26572 Carretas, Mission Viejo, CA 92691 (US). (74) Agents: VOET, Martin, A. et al.; Allergan, Inc., 2525 Dupont Drive, Post Office Box 19534, Irvine, CA 92713-9534 (US).		(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published <i>With international search report.</i> <i>With amended claims and statement.</i>
(54) Title: COMPOSITIONS COMPRISING A DRUG DELIVERY VEHICLE SUSPENDED IN A NONAQUEOUS FLUORINATED LIQUID (57) Abstract Nonaqueous pharmaceutical compositions for use in aqueous physiological systems are disclosed comprising drug delivery vehicles suspended in nonaqueous perfluorocarbon or fluorinated silicone liquid carriers. The suspended drug delivery vehicles may be water labile or water stable and incorporate therapeutic or diagnostic compounds which remain stable and pharmaceutically effective for extended periods. The pharmaceutical compositions have improved bioavailability, are capable of low dose volume delivery, and do not leach the incorporated therapeutic or diagnostic compounds into the liquid carriers making them well suited for multi-dose packaging and administration.		

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COMPOSITIONS COMPRISING A DRUG DELIVERY VEHICLE SUSPENDED IN A NONAQUEOUS FLUORINATED LIQUID

5 Reference of Earlier Application

This application is a continuation-in-part of copending application Serial No. 07/588,697, filed September 27, 1990.

10 Field of the Invention

The present invention relates in general to nonaqueous pharmaceutical compositions intended for use in aqueous physiological systems. More particularly, the present invention is directed to pharmaceutical
15 compositions formed of drug containing microparticulate or microcapsule delivery vehicles suspended in perfluorocarbons or fluorinated silicone liquids. The pharmaceutical compositions of the present invention possess unexpectedly superior shelf-lives, increased
20 bioavailability, prolonged drug delivery profiles and may be configured for convenient multi-dose administration through common routes of pharmaceutical administration including advantageously small volume drop installation administration.

25

Background of the Invention

Pharmaceutical medicaments and diagnostic compounds are frequently incorporated into a delivery vehicle for administration to a targeted tissue site. Typically, drug
30 delivery vehicles are formed as aqueous carriers, gels, polymeric material inserts or particulates incorporating a pharmaceutical compound. Once the drug delivery vehicle is placed at the desired delivery site, the pharmaceutical compound is released from the delivery vehicle over a
35 prolonged length of time. The resulting time release profile of the drug is dependent upon a number of variables. Included in these variables are the release mechanism of the drug from the drug delivery vehicle (typically either erosion or diffusion), the amount of

drug incorporated into the drug delivery vehicle, the solubility of the drug in the surrounding physiological milieu, and, in the case of particulate delivery vehicles, the particle size or size distribution of the vehicle.

5 Depending upon the physical characteristics of the vehicle itself as well as those at the intended target site, drug delivery vehicles may be delivered to the target site through a variety of known routes of administration. For example, aqueous based drug delivery
10 solutions may be ingested, injected, inhaled, or applied directly to the skin or mucus membranes as drops, mists, or the like. Conversely, gels and ointments are better suited to direct topical application due to their relatively high viscosities. Similarly, solid polymeric
15 inserts must be physically inserted or affixed to the target site.

A particularly unique target site for pharmaceutical compounds is the ocular environment surrounding the surface of the eye. Aqueous solutions, gels and solid
20 inserts have all been utilized to deliver ocular drugs as the controlled delivery rate characteristics of such known delivery vehicles make them well suited for delivering therapeutic and diagnostic compounds to the ocular environment. However, tear turnover and drainage through
25 the lacrimal system quickly remove a major portion of any compound administered as a drop to the eye so that only a small fraction of the original dosage remains in the eye long enough to be of therapeutic impact. Moreover, unnecessarily high liquid dose volume inherent in water
30 and oil based delivery systems result inefficient use of drug delivery compositions. Thus, repeated administrations of a drug formulated as an aqueous drop may be required to maintain an effective therapeutic level of the drug in the eye. Thus, pharmaceutical compositions such
35 as ointments, gels or inserts which remain in the eye and gradually release their diagnostic or therapeutic drugs

into the ocular environment reduce the need for repeated administrations of the drug to the eye.

Recently, drug delivery vehicles formed of drug-containing erodible microparticles or microcapsules have
5 been developed with some limited success. Such erodible microparticles or microcapsules are designed to be suspended in a liquid carrier medium and delivered to the target tissue through injection, ingestion or using liquid drops. Once at the target site the microparticulates or
10 microcapsules are intended to remain at that location after the liquid carrier has diffused or drained away. Typically, microparticulates are formed of a drug containing polymer matrix formed in particles ranging from tens to hundreds of microns in diameter. The polymer
15 matrix may be erodible to release the incorporated drug at the target site as the matrix gradually breaks down. Alternatively, the microparticulates may be formed of non-erodible polymers from which the incorporated drug simply diffuses out of and into the target tissue. Microcapsules
20 are comparably sized particles formed of a polymer shell encapsulating the desired pharmaceutical compound. The shell of microcapsules may also be composed of either erodible or non-erodible polymers.

The long term storage of microparticles and
25 microcapsules requires a liquid carrier medium which is physically and chemically compatible with both the polymer of the drug delivery vehicle and the incorporated therapeutic or diagnostic compound as well as the intended physiologic environment. Generally, the liquid carrier of
30 choice is a sterile water solution of the appropriate pH and osmolality. However, a problem with suspending microparticles or microcapsules in aqueous carriers targeted for an aqueous physiological environment is that invariably the incorporated pharmaceutical compound will
35 leach into the aqueous carrier prior to administration. This results in a significant loss of pharmaceutical activity at the site of action as the leached drug

contained in the aqueous carrier will be flushed from the target site relatively rapidly.

The tendency of pharmaceutical compounds to leach into the carrier also limits the effective shelf-life of drug delivery vehicles suspended in aqueous carriers. Depending upon the diffusion rate of the incorporated pharmaceutical compound, the shelf-life will normally be much shorter than the preferred shelf-life. Similarly, diffusion of the drug into the aqueous carrier makes it difficult, if not impossible, to formulate pharmaceutical compounds into multiple dose packaging because uniform dose regimens cannot be ensured.

More specifically, pharmaceutical compositions containing drug delivery vehicles utilizing a polymer or drug which is unstable or labile in an aqueous environment cannot be stored for extended lengths of time in their aqueous carriers without significant chemical changes occurring. A significant number of the polymers which are currently being utilized as microparticulate drug delivery vehicles are hydrolytically labile. This characteristic is central to the ability of the polymer matrix to slowly disintegrate and release the drug incorporated in the polymer matrix into the aqueous physiological environment. Since the polymer systems exhibiting hydrolytic instability cannot be stored in aqueous vehicles, they must be stored in a dry state and suspended in the aqueous carrier immediately prior to their administration to the target site. This is a time consuming and burdensome inconvenience to the end user. Moreover, it requires specialized packaging designs which provide a method for separately storing the labile polymer particles and the carrier liquid in appropriate quantities. As a result, the package configuration must be limited to unit dose sizes with the attendant inconvenience and added costs.

Several nonaqueous liquid carriers have been utilized in the art in an attempt to address these problems. Among these are mineral oils, vegetable oils, silicone oils, and

free fatty acids. Though generally effective for oral and dermal administration, when used in the ocular environment a significant disadvantage associated with these oils is that they combine with the lipid layer of the tear film which results in a disruption of the film. This in turn may cause the user to experience significant vision blurring and an unacceptable oily sensation. Even if the tear film is not disrupted, the significant difference in the refractive index of the tear film and the refractive index of the oil carrier causes blurring during the residence time of the oil.

A related drawback associated with the ophthalmic drop instillation delivery of pharmaceuticals incorporated in water or oil carrier systems is that conventional small volume droppers have relatively limited delivery volumes restricted to drop sizes that may interfere with vision or be uncomfortable to the user. This is because the density and surface tension characteristics of the typical water and oil based systems do not allow for the practical delivery of less than 35 μ l volumes. Thus, because the eye tear film can accommodate only about a 7 μ l volume of liquid, when amounts greater than this are delivered to the eye the excess liquid will disrupt the tear film and may be rapidly blinked away. This results in the inefficient and costly loss of both liquid carrier and pharmaceutical agent.

Accordingly, it is a principal object of the present invention to provide pharmaceutical compositions which will effectively deliver water labile or poorly soluble therapeutic or diagnostic pharmaceutical compounds to aqueous physiological target sites through a wide variety of administrative routes including ingestion, injection, inhalation, topical application, sprays, mists, drops and the like. It is a further object of the present invention to provide pharmaceutical compositions for delivering water labile or poorly soluble therapeutic or diagnostic

pharmaceutical compounds which exhibit improved shelf-life and stability.

It is an additional object of the present invention to provide drug delivering pharmaceutical compositions in which the therapeutic or diagnostic compounds do not prematurely leach out of the drug delivery vehicles during storage yet are released at the desired rate once administered to the target site.

It is a further object of the present invention to provide drug delivering pharmaceutical compositions intended for use in aqueous physiological systems which may be configured in multi-dose packages.

It is another object of the present invention to provide drug delivering pharmaceutical compositions capable of forming drop sizes on the order of 10 μ l when delivered from standard dropper bottles.

It is also an object of the present invention to provide drug delivering pharmaceutical composition having improved efficiency of delivery.

It is an additional object of the present invention to provide pharmaceutical compositions containing hydrolytically labile polymers or drugs which are intended for use in aqueous physiological milieus which are protected from premature disintegration.

It is a further additional object of the present invention to provide effective pharmaceutical compositions which are transparent, nonirritating, and do not cause vision blurring when administered to the ocular environment.

30

Summary of the Invention

The present invention accomplishes these and other objectives by providing advantageous pharmaceutical compositions formed of drug delivery vehicles suspended in nonaqueous liquid carriers for low dose volume delivery. The pharmaceutical compositions of the present invention have improved bioavailability, provide efficient delivery

of drugs in the form of low dose volumes and possess long shelf-lives with retained pharmaceutical activity and may be packaged in multi-dose configurations. Additionally, they can be formulated to stably incorporate hydrolytically labile drugs and polymers and may be administered to intended target sites through any available route of administration including small volume drop instillation methods. Unlike prior art drug delivery systems, the pharmaceutical compositions of the present invention can be delivered in dose volumes of less than 10 μ l, resulting in improved drug delivery efficiency and increased bioavailability.

In accordance with the teachings of the present invention, low volume pharmaceutical compositions are preferably formed from a perfluorocarbon or fluorinated silicone liquid carrier and at least one drug delivery vehicle incorporating the desired therapeutic or diagnostic compounds. It is also contemplated as being within the scope of the present invention to form the drug delivery vehicle of polymeric particulates suspended in nonaqueous liquid carriers wherein the polymeric drug delivery vehicles incorporate a pharmaceutically effective amount of the desired therapeutic or diagnostic compounds. Preferably, the polymeric drug delivery vehicle is formed as a plurality of erodible microparticles or microcapsules which incorporate the compound of choice and are suspended in the nonaqueous liquid carrier. As those skilled in the art will appreciate, mixtures of differing erodible microparticles and microcapsules can be combined in a single carrier within the scope of the present invention to tailor the pharmaceutical composition to specific drug contents, polymer erosion rates, and drug release profiles.

Due to the nonaqueous character of the liquid carriers utilized in the pharmaceutical compositions of the present invention they are particularly suitable for suspending polymeric drug delivery vehicles prepared with

hydrolytically labile polymers or pharmaceutical compounds. However, pharmaceutical compositions comprising hydrolytically stable polymeric drug delivery vehicles or pharmaceuticals are also within the scope of
5 the present invention.

Unlike the prior art delivery systems, the pharmaceutical compositions of the present invention possess stable, long term shelf-lives without the associated loss of pharmaceutical activity of the
10 therapeutic or diagnostic compound incorporated therein. This stability results from the fact that the therapeutic or diagnostic compound does not leach or otherwise diffuse from the microparticulates or microcapsules into the liquid carrier, but remains incorporated in the drug
15 delivery vehicle. Similarly, where the microparticulates or microcapsules are formed of water labile polymers, they will not erode or degrade in the compositions of the present invention.

Moreover, unlike prior art aqueous and oil based
20 delivery systems, which are limited to a minimum of about 35 μ l drop sizes, the pharmaceutical compositions of the present invention form low volume doses of less than 10 μ l. The pharmaceutical compositions of the present invention, preferably consisting of microparticulate or
25 microcapsule drug delivery vehicles suspended in the liquid carriers, may be packaged and sterilized by conventional gamma irradiation techniques. Sterile fill procedures are available as an alternative to radiation sterilizing techniques. Additionally, the pharmaceutical
30 compositions can be configured for multiple or unit dose packaging from, for example, a dropper dispenser. The unique bacteriostatic properties of the liquid carriers further facilitate the utilization of multi-dose packaging by eliminating the necessity of preservative additives
35 commonly used in the art.

As will be discussed below, a wide variety of polymers and therapeutic and diagnostic agents can be

utilized in forming the compositions of the present invention. Polymers and agents which are hydrolytically labile are particularly suitable, however, the advantageous properties of the nonaqueous compositions can
5 be obtained with hydrolytically stable drug delivery vehicles as well.

Further objects and advantages of the nonaqueous pharmaceutical compositions of the present invention, as well as a better understanding thereof, will be afforded
10 to those skilled in the art from a consideration of the following detailed description of preferred exemplary embodiments thereof.

Brief Description of the Drawings

15 FIG. 1 is a graphical representation of the release profile of sodium fluorescein from a microparticulate suspension stored at 23°C illustrating the principles of the present invention.

FIG. 2 is a graphical representation of the release
20 profile of sodium fluorescein from a microparticulate suspension stored at 45°C illustrating the principles of the present invention.

FIG. 3 is a graphical representation of the temperature stability profile of a water labile drug
25 containing microparticulate suspension stored at 37°C illustrating the principles of the present invention.

FIG. 4 is a graphical representation of the temperature stability profile of a water labile drug containing microparticulate suspension stored at 23°C
30 illustrating the principles of the present invention.

Detailed Description of the Preferred Embodiments

In a broad aspect, the low volume, efficient pharmaceutical compositions of the present invention
35 comprise one or more drug delivery vehicles suspended in a perfluorocarbon or fluorinated silicone nonaqueous liquid carrier. More particularly, the pharmaceutical

compositions produced in accordance with the teachings of the present invention can be formed from a perfluorocarbon or fluorinated silicone liquid carrier and, suspended in the liquid carrier, at least one drug delivery vehicle
5 incorporating a pharmaceutically effective amount of at least one therapeutic or diagnostic compound.

Because of the bacteriostatic, nonirritating, and in fact, soothing and lubricating properties of the nonaqueous liquid carriers, the pharmaceutical
10 compositions formed in accordance with the teachings of the present invention are particularly well suited for use in connection with the diagnosis or treatment of injuries or diseases of the eye. Further advantages associated with their ophthalmic utility are the low surface tension
15 and high density of the nonaqueous liquid carriers, which allow for small volume drop delivery. However, those skilled in the art will appreciate that the pharmaceutical compositions of the present invention are equally well suited for use in applications to other physiological
20 environments where the repeated administration of a drug delivery vehicle to sensitive tissue areas is desired.

Accordingly, for purposes of explanation and without limiting the scope of the present invention, where appropriate the following exemplary embodiments will be
25 discussed in the general context of ophthalmic pharmaceutical compositions utilized for the treatment of ocular injuries and diseases. However, it should be emphasized that the pharmaceutical compositions of the present invention may be utilized through all common
30 routes of administration such as oral, dermal, intravenous, nasal and others known in the art.

The perfluorocarbons which are preferably utilized as nonaqueous liquid carriers in the low volume, high efficiency pharmaceutical compositions of the present
35 invention include perfluorocyclocarbons, acyclic perfluorocarbons and their derivatives. As one skilled in the art will appreciate, the perfluorocarbon derivatives

are typically nitrogen and oxygen containing compounds such as amines and ethers. The nonaqueous liquid carrier compounds, however, are preferably perfluorinated, meaning that all of the hydrogens bonded to the carbons of the compound are substituted with fluorine. Thus, perfluorinated cyclic and acyclic hydrocarbons as well as the amine and ether derivatives of these compounds may be utilized in the pharmaceutical compositions of the present invention.

Exemplary perfluorocarbons which are particularly suitable for use in the pharmaceutical compositions of the present invention are blood substitutes. Perfluorocarbon blood substitutes include perfluorodecalin, perfluoroperhydrophenanthrene, perfluoromethylcyclohexane, perfluoro-1-methyldecalin, perfluoro(1,3-dimethylcyclohexane), perfluorotrimethylcyclohexane, perfluoroisopropylcyclohexane, perfluoroendotetrahydroadipic acid, perfluoro-1-methyl-4-isopropylcyclohexane, perfluoro-1-methyl-4-isopropylcyclohexane, perfluoro-n-butylcyclohexane, perfluoro(decahydronaphthalene), perfluoro(decahydro-1-methylnaphthalene), perfluoro(decahydrodimethylnaphthalene), perfluoromethyladamantane, perfluorotrimethylbicyclo(3.3.1.)nonane, perfluorodimethylbicyclo(3.3.1.)nonane, perfluoro-1-methyldecaline. Oxygen and nitrogen containing derivatives of perfluorocarbons which may be used as liquid carriers include perfluorotributylamine, perfluorotriisopropylamine, perfluorotetrahydrofuran and perfluoroether.

Exemplary fluorinated silicone oils for use in practicing the present invention are the polyalkylfluoroalkylmethylsiloxanes. In particular, the polytrifluoropropylmethylsiloxanes with molecular weights of between 500 and 14,000 are suitable for use in the pharmaceutical compositions of the present invention.

Preferred perfluorocarbons and fluorinated silicones have vapor pressures sufficiently low to prevent significant liquid loss caused by their evaporation from containers during storage. Fluorinated liquid carriers having ambient pressure boiling points greater than 100°C are preferred to ensure that any evaporative losses are less than that observed for water. Additionally, exemplary preferred perfluorocarbons and fluorinated silicones have a rapid elimination half-life. Less desirable perfluorocarbons are known to reside in fat tissues for as long as 2 - 3 years. Perfluorodecalin (PFD) and perfluoroperhydrophenanthrene (PPP) are preferred perfluorocarbons because of their relatively high ambient pressure boiling points, 142°C and 215°C, respectively. Additionally, PFD and PPP have quite rapid elimination half-lives when a systemically administered with the half life of PFD being about 7 days.

An additional aspect of the present invention involves suspending a polymeric drug delivery vehicle incorporating a pharmaceutically effective amount of at least one diagnostic or therapeutic compound in the perfluorocarbon or fluorinated silicone nonaqueous liquid carrier. Preferably, the polymeric drug delivery vehicle is in the form of a plurality of erodible microparticulates, each sized on the order of approximately 2 microns to 200 microns or, alternatively, a plurality of microcapsules sized on the order of approximately 20 microns to 200 microns. However, larger drug delivery vehicles such as ocular inserts are also contemplated as being within the scope of the present invention. It is also within the scope of the present invention to prepare pharmaceutical compositions comprising a mixture of particle sizes or mixtures of microcapsules and microparticulates with varying erosion rates. Such combinations can be designed to provide specific drug release profiles including high initial concentrations or so called zero order deliveries or may

be utilized to provide combinations of different pharmaceutical compounds.

The solid or suspended drug delivery vehicles utilized in the pharmaceutical compositions of the present invention can be prepared through a variety of methods known to those skilled in the art. Exemplary methods for preparing microparticulates include grinding or milling mixtures of an appropriate polymer and therapeutic or diagnostic drug. Alternative methodologies include grinding or milling the polymer to form microparticulates and subsequently absorbing the drug of choice into the microparticulates so produced. Microencapsulation techniques in which emulsions of the polymer and therapeutic or diagnostic compound are coacervated to precipitate the polymer and encapsulate the compound also can be used to form microcapsule drug delivery vehicles for use in the present invention. Non-limiting examples of such formation techniques are provided below.

20

EXAMPLE 1

A general method for the manufacture of microparticulates involves the preparation of a stock polymer solution using 0-30% drug (preferably 0-10%) such as dipivefrin by first adding the drug to the solvent of choice such as acetone, acetonitrile, dimethylformamide, or ethyl acetate. The drug and solvent are combined and the mixture is stirred as the polymer (preferably poly(methylvinylether/maleic anhydride)) is added so polymer clumping is avoided. Mixing continues until the polymer is completely dissolved. The drug need not be completely dissolved in the solvent/polymer system, but the drug particles must be homogeneously dispersed. The mixture is then transferred to a roto-evaporator and the solvent is slowly removed. The temperature should not

exceed 60°C. When all solvent is removed, the film is ground in the presence of dry ice with a small blade grinder until the appropriate sized range is achieved: 2-200µm. For example, 5 g of poly(methylvinylether/maleic anhydride) is completely dissolved in a solution containing 100 mg dipivefrin in 95 ml of acetonitrile. This polymer stock is then added to a roto-evaporator operating at 40°C, and the acetonitrile is completely removed. The drug/polymer residue is removed from the evaporator flask and placed in a Teckmar grinder along with dry ice particles. The dry ice facilitates grinding, and the grinding takes approximately 2 minutes.

EXAMPLE 2

Alternatively, the drug/polymer stock mixture from Example 1 is roto-evaporated to dryness and the residue is first ground in a mortar and pestle and placed in a roller bottle containing glass beads with a nonaqueous diluent (preferably perfluorodecalin, PFD). The suspension is ball milled for approximately three days to reach the desired 2-200µm size range.

EXAMPLE 3

Alternatively, the drug/polymer stock mixture from Example 1 is added dropwise with agitation to an immiscible liquid (preferably mineral oil) containing 0-10% emulsifier (preferably lecithin). Microparticles are formed as polymer stock is dispersed in the immiscible phase and the polymer solvent is evaporated. Other immiscible liquids include vegetable oils, silicone oils, and

perfluorocarbons. The ratio of polymer stock solution to immiscible phase should not exceed 1:3 v/v. The final particle size distribution of the particles is dependent on the degree of agitation and the viscosity of the immiscible material. Generally, a pneumatic mixer rotating at approximately 300 rpm gives the desired particle size range. Once all of the polymer solvent is evaporated from the particles, the particles are cleaned several times with a solvent, typically hexane.

Exemplary polymers suitable for incorporating therapeutic or diagnostic compounds in accordance with the teachings of the present invention are those polymers which are compatible with both the target tissue and with the therapeutic or diagnostic compound of choice. Included within this class of polymers are both hydrolytically stable and hydrolytically labile polymers. Those skilled in the art, however, will appreciate that polymeric drug delivery vehicles prepared from polymers which are hydrolytically labile are particularly well suited for use with the perfluorocarbons or fluorinated silicone carriers of the present invention as they are stable in solution yet will erode in the aqueous environment of the target site and thereby eliminate themselves from the site as their pharmaceutical compounds are delivered.

Exemplary hydrolytically stable polymers which are suitable for use in the polymeric drug delivery vehicles include acrylate, ethylene vinylacetate, silicones, polyurethanes, and polysulfones. Exemplary polymers which are labile in an aqueous environment include poly(methylvinylether/maleic anhydride), polyfumaric acid/sebacic acid, collagen, gelatin, polyvinyl alcohol, methylcelluloses, polyorthoesters, polyglycolic acid, polylactic acid, polyvinylpyrrolidone, polysebacic acid anhydride,

polycarboxyphenoxypropane anhydride, polyterephthalic acid anhydride, and polyphosphazine.

A preferred exemplary aqueous labile polymer is Gantrez AN, a Poly(methylvinylether/maleic anhydride) available from GAF. Upon contact with an aqueous medium the anhydride functionalities of this polymer readily hydrolyze to form the free acid. This initial hydrolysis leads to the formation of a hydrogel with soft bioadhesive properties. As hydrolysis proceeds, the poly(methylvinylether/maleic anhydride) dissolves, and during the dissolution process the incorporated drug is continuously released. However, in accordance with the teachings of the present invention, pharmaceutical compositions prepared from Gantrez AN microparticulate or microcapsule drug delivery vehicles suspended in a perfluorocarbon carrier do not prematurely erode and release the incorporated drug. Similarly, they do not release the incorporated drug during storage and provide a long-shelf life, yet they are very effective when delivered to the aqueous target environment.

An alternative hydrolytically labile polymer drug delivery system can be formed from those compounds which have ionic side chains capable of complexing with a drug of opposite ionic charge. Microparticulates formed of these polymers erode in the aqueous physiological environment and dissociate the drug which is ionically bound to the polymer thereby delivering the drug to the target site. Pharmaceutical compositions prepared from these ionic polymers suspended in a nonaqueous carrier such as perfluorocarbon do not prematurely release the ionically bound drug and therefore can be prepared in stable, multi-dose forms.

Any pharmaceutical compound which is suitable for therapeutic or diagnostic purposes and is compatible with a suitable polymer may be incorporated in the drug delivery vehicle of the present invention. Exemplary pharmaceutical compounds included protein growth factors,

oligopeptides, antibacterial, antihistaminic, anti-inflammatory, miotic, anticoloneurgic, mydriatic, antiglaucoma, antiparasitic, antiviral, carbonic anhydrase inhibitor, antifungal, anesthetic, diagnostic and immunosuppressive agents. Preferred pharmaceutical compounds for use in ocular situations include epithelial growth factor, dipivalyl epinephrine hydrochloride (DPE), levo-bunolol hydrochloride, UK-14304-18, pilocarpine, dipivefrin, sodium fluorescein, tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, tobramycin, ciprofloxacin, norfloxacin, penicillin, erythromycin, cefazolin, ceftazidime, imipenem, idoxuridine, hydrocortisones, dexamethasone, dexamethasone 21 phosphate, fluocinolone, medrysone, prednisolone acetate, fluormetholone, betamethasone, trimeinolone, phenylephrine, eserine salicylate, carbachol, phospholine iodide, demecarium bromide, cyclopentolate, homotropine, scopolamine, epinephrine, ibuprofen, aceclidine, tretinoin, and catalin.

The amount of therapeutic or diagnostic compound incorporated in the polymer is dependent upon the compound of choice, the required dose, and the form of the drug delivery vehicle. The effective amount normally ranges from a few percent up to 60% by weight of the polymer with microparticles generally having smaller amounts than microcapsules.

Contributing to the economies of the present invention, the pharmaceutical compositions may be prepared by methods known in the art for formulating drug delivery vehicles suspended in a liquid carrier. The amount of drug delivery vehicle suspended in the carrier liquids of the present invention depends upon the dose configuration and the desired dose volume. For single dose units packaged in dropper style delivery systems the volume ratio of carrier liquid to microparticulate ranges from about 99.0 to about 5.0. Volume ratios for packaging configurations designed for multiple uses typically range

from about 99.9 to about 3.0 liquid carrier to microparticulate. Preferably, the weight to volume ratio of suspended drug delivery vehicle to nonaqueous carrier liquid will range from approximately 0 to 10%. However, 5 those skilled in the art will appreciate that these ratios are appropriately adjusted to adapt to the intended applications, target sites and pharmaceutical compounds utilized in accordance with the teachings of the present invention.

10 Preferably, the low volume, high efficiency pharmaceutical compositions of the present invention are finally packaged in sterile condition. This may be achieved through formulation procedures utilizing sterile fill methods and heat or gamma irradiation techniques to 15 obtain a sterile product. One exemplary approach to producing a sterile pharmaceutical composition may be utilized when the desired microparticulate size is obtained with wet milling procedures utilizing a nonaqueous liquid carrier. Such a procedure includes 20 sterilizing the drug/polymer stock powder mixture using a suitable sterilizing method such as heat or gamma irradiation, and sterile filtering the selected perfluorocarbon or fluorinated silicone. The sterile drug/polymer stock powder is then aseptically combined 25 with the sterile nonaqueous liquid carrier and the mixture is wet milled until the desired particle size is reached. The final product is then aseptically filled into the desired package configuration.

Another procedure for obtaining sterile 30 pharmaceutical compositions of the present invention includes dry milling drug/polymer stock to the desired particle size followed by sterilizing the resulting microparticulates. The sterile dry powders are then aseptically added to a previously sterile filtered 35 perfluorocarbon or fluorinated silicone.

The following additional non-limiting examples are illustrative of methods used for formulating the pharmaceutical compositions of the present invention.

5

EXAMPLE 4

To produce a microparticulate drug delivery vehicle suspended in a nonaqueous carrier the dry powder microparticulate drug delivery vehicles produced from the grinding procedure of the Example 1 are simply added to perfluorodecalin in a preferred ratio of from 0 to 10% w/v. Sonic agitation may be utilized to assist in the even distribution of the microparticulates.

15

EXAMPLE 5

Alternatively, the microparticulate drug delivery vehicle produced utilizing the ball milling procedure of Example 2 can be utilized as follows. As a preliminary step the drug containing microparticulates are separated from the glass beads of the ball mill. Where the nonaqueous diluent in the ball milling procedure is the preferred nonaqueous carrier liquid, such as perfluorodecalin the separated microparticulate suspension is simply diluted to the desired concentration, preferably ranging from approximately 0 to 10% w/v utilizing addition of perfluorodecalin. As those skilled in the art will appreciate, where alternative grinding solvents are utilized additional separation may be necessary as is known in the art prior to preparing the suspension.

30

EXAMPLE 6

Alternatively, microparticulate drug delivery vehicles produced through the emulsion technique of Example 3 may be utilized to form the pharmaceutical compositions of the present invention as follows. Once the microparticulates produced through solvent evaporation are washed with the appropriate solvent, preferably hexane, the microparticulates are dried in a vacuum oven until all residual hexane is removed. The dried particles are simply added to perfluorodecalin or other nonaqueous carrier liquids in the desired proportions, preferably ranging from approximately 0 to 10% w/v.

It is additionally contemplated as being within the scope of the present invention to incorporate surfactants and/or suspending agents in the pharmaceutical compositions. The presence of surfactants or suspending agents assists in the formation of stable uniform suspension of microparticulates in perfluorocarbon or fluorinated silicones. Stable suspensions in turn contribute to the ability to deliver a consistent, low volume dose regimen over the life of the pharmaceutical composition. Suitable exemplary pharmaceutically acceptable surfactants include non-ionic ethoxylated alcohols and sorbitans. Included in the group of acceptable surfactants are the Pluronic, Tweens, Polyethylene glycols, Spans, lecithin and oleic acid which act to neutralize residual static charges on the particles and to prevent aggregation. Suspending agents include simple sugars, salts, synthetic polymers, polysaccharides and celluloses, etc., which act to prevent particle settling through steric collisions. Which suspending agents and surfactants are preferred will be dependent upon the particular polymer and perfluorocarbon or

fluorinated silicone utilized routine in a specific pharmaceutical composition and can be determined utilizing stability testing procedures.

As will be appreciated by those skilled in the art, the exemplary perfluorocarbon and fluorinated silicone liquids utilized in the pharmaceutical compositions of the present invention provide unique chemical and physical properties which make them particularly well suited for use as nonaqueous liquid carriers for polymeric drug delivery vehicles. More particularly, they are chemically and physically stable. Thus, drug delivery vehicles prepared from virtually any suitable polymer and drug combination may be suspended in the perfluorocarbon or fluorinated silicone liquid carriers for extended periods of time without unwanted interactions between the carrier and the polymer or drug.

In addition to these enhanced liquid storage properties, the pharmaceutical compositions produced in accordance with the techniques of the present invention also have unexpectedly improved shelf-lives when compared with pharmaceutical compositions stored in a sterile, dry state. It is believed that the hydrophobic nature of the compositions precludes small amounts of oxygen and moisture from gaining access to the drug delivery vehicles, and thus they remain viable and pharmaceutically active for an extended period of time.

In contrast, prior art drug delivery vehicles formed from hydrolytically labile polymers can not be suspended for long term storage in aqueous carriers. Normally, these vehicles are packaged and stored in the dry state in order to achieve reasonable shelf-lives. Users of drug delivery vehicles which are stored without the benefit of being suspended in a carrier liquid are inconvenienced by the necessity of having to suspend the vehicles in a sterile aqueous carrier just prior to delivery to the target site.

The perfluorocarbon or fluorinated silicone suspension vehicles utilized in the present invention provide a unique and advantageous alternative to storing labile microparticles or microcapsules in the dry state.

- 5 The pharmaceutical compositions prepared in accordance with the present invention are "user friendly" in that they are available in ready to use pre-mixed preparations.

As noted above, an equally beneficial property of the
10 pharmaceutical compositions of the present invention is their ability to remain stable for a long period of time without leaching or loss of the pharmaceutical compound from the polymeric drug delivery vehicle into the liquid carrier. The pharmaceutical compounds are effectively
15 locked in to the delivery vehicle until the formulation is administered to the desired physiological site. There, the nonaqueous carrier solution is replaced by the aqueous physiological fluid at the target site which initiates release of the incorporated pharmaceutical compound.

- 20 This is specially important when the polymeric drug delivery vehicle utilized to form the pharmaceutical composition is a hydrolytically labile polymer. As those skilled in the art will appreciate, hydrolytically labile polymers are characterized by their ability to physically
25 or chemically erode in an aqueous environment. This erosion occurs over a period of time by any of a number of different processes such as enzymatic degradation, hydrolysis, or solubilization in response to contact with an aqueous physiological environment. Thus, when a drug
30 delivery vehicle which is formed from a hydrolytically labile polymer and an incorporated pharmaceutical compound is placed in the ocular environment, it erodes in a manner that results in the release or delivery of the drug to the eye.

- 35 The following examples are illustrative of the enhanced shelf life and prolonged stability of exemplary

pharmaceutical compositions produced in accordance with the teachings of the present invention.

EXAMPLE 7

5 In order to determine the temperature stability and release profile of the nonaqueous drug delivery vehicle suspensions of the present invention microparticulates containing 5% sodium fluorescein were prepared utilizing
10 poly(methylvinylether/maleic anhydride) as the polymer matrix utilizing the manufacturing technique of Example 1 and were suspended in perfluorodecalin as a 2% w/v suspension utilizing the technique of Example 4. This
15 nonaqueous drug delivery vehicle suspension was divided in half and equal portions were stored at 23°C and at 45°C for thirty days. Samples were taken of each portion during the thirty day test period and fluorescein release profiles
20 were obtained as is known in the art. More specifically, the dissolution tests were performed as follows. 500 ml of 7.4 pH phosphate buffer (0.05M) was added to the kettles in the standard USP dissolution
25 apparatus set at 37°C. 10 ml of the 2% w/v suspension was slowly added to the dissolution medium and the propeller speed was set to 50 rpm. Over a seven hour time period, samples were taken from the dissolution medium and
30 immediately centrifuged. The supernatant containing the released fluorescein was assayed for fluorescein content by UV spectrophotometry. Release profiles for the 23°C and 45°C samples are given in FIGS. 1 and 2.

EXAMPLE 8

An additional set of experiments was performed to determine if a water labile drug was stable in the suspended drug delivery vehicle when stored in the preferred nonaqueous carrier liquid, perfluorodecalin. Microparticulates containing 2% dipivefrin were prepared from three different lots of poly(methylvinylether/maleicanhydride) obtained from GAF, Inc. (Lot #8277, 8555, and 8609) utilizing the microparticulate production technique of Example 1. The ground microparticulates were added to perfluorodecalin to form a 5% w/v suspension. As with Example 7, portions of this suspension were stored at different temperatures for thirty days. One portion was stored at 23°C (essentially ambient temperature) and a second portion at 37°C. At various intervals during this thirty day period samples were taken from each portion and the microparticulates were extracted from the perfluorodecalin phase using acetonitrile. The content of undegraded dipivefrin and known degradants in the acetonitrile phase were then assayed using HPLC. Results of these experiments are given in FIGS. 3 and 4.

As those skilled in the art will appreciate, the foregoing examples illustrate the outstanding long-term storage stability of the pharmaceutical compositions of the present invention as well as the consistent drug release rates following storage at varying temperatures.

Advantageously, the nonaqueous liquid carriers utilized to form the low volume pharmaceutical compositions of the present invention are soothing, non-irritating and non-toxic. Thus, their use in physiological applications, and in particular the ocular

environment, is particularly suitable. The experiment described in Example 9 illustrates and confirms this non-toxicity of an exemplary pharmaceutical composition of the present invention.

5

EXAMPLE 9

In order to evaluate the in vivo toxicity characteristics of the pharmaceutical composition of the present invention, an in vivo toxicity probe study was performed in rabbit eyes. Microparticles of 5 w/w% DPE in Gantrez AN169 (a polyvinylether maleic anhydride) were prepared and suspended in perfluorodecalin. Two suspensions were studied, the first contained 2 w/v% microparticulate in perfluorodecalin and the second contained 5 w/v% microparticulate in perfluorodecalin. Because Gantrez AN169 is water labile, no comparable study in an aqueous suspension was possible. Each suspension was administered to rabbit eyes and no adverse effects were observed.

As an added benefit, the pharmaceutical compositions of the present invention can be packaged for multi or single dose use. The availability of the option for multi-dose packaging is a significant advantage over single dose or unit dose packaging which is required for many pharmaceutical compositions. Single dose packing is more costly and many users prefer the convenience of, for example, large volume eye dropper delivery designs for multi-dose applications.

Additionally, unlike aqueous based pharmaceutical compositions which will support the growth of bacteria if preservatives are not used, the pharmaceutical compositions of the present invention have bacteriostatic properties. These bacteriostatic properties make it possible to provide pharmaceutical compositions without

preservative additives and the possible side effects thereof. This is particularly advantageous for users of ophthalmic preparations who have a sensitivity to preservatives. Additionally, when the pharmaceutical compositions of the present invention are packaged in multi-dose configurations they can be sterilized once and then repeatedly opened and reused without fear of the subsequent growth of harmful organisms in the liquid carrier.

Other beneficial characteristics of the pharmaceutical compositions of the present invention derive from their ability to operate in the ocular environment with minimal vision disruption. The nonaqueous carriers utilized in the pharmaceutical compositions have refractive indices which are very close to that of water. What is more, they are immiscible with both the lipid layer and the aqueous layer of the ocular tear film. This immiscibility reduces disruptive interaction with the tear film layers. Additionally, the advantageously small drop size and nearly identical refractive indices of the nonaqueous compositions and the aqueous layer of the tear film substantially eliminates the vision perturbation commonly associated with the use of current nonaqueous pharmaceutical carriers such as mineral oils.

As an added functional benefit, the preferred perfluorocarbon carriers have specific gravities in excess of 1.2. As a result, when utilized in conjunction with suspended microparticles or microcapsules delivered to the cul-de-sac of the eye, this relatively high specific gravity, coupled with the carriers' immiscibility with the aqueous layer of the tear film, causes the carrier to separate rapidly from the particulate vehicle and to drain from the eye through the lacrimal duct while leaving the slow release carrier in the intended aqueous environment.

In accordance with the teachings of the present invention, the pharmaceutical composition so produced may

be utilized to deliver therapeutic or diagnostic agents to physiological target sites including the eye or other similar environments through any currently available administration route.

5 An exemplary method for delivering therapeutic or diagnostic compounds comprises the steps of providing a pharmaceutical composition of a perfluorocarbon liquid carrier and at least one therapeutic or diagnostic drug containing delivery vehicle suspended therein and
10 administering a low volume yet effective dosage of the pharmaceutical composition to the target site. The administration route can be through injection, oral ingestion, nasal inhalation, topical application, eye drops or any other currently available administration
15 route due to the broad applicability of the compositions of the present invention.

The beneficial delivery characteristics of the low volume, high efficiency pharmaceutical compositions of the present invention are produced by the physical properties
20 of the fluorinated liquid carriers. More specifically, the high densities (typically greater than 1.2) and low surface tensions of perfluorocarbons and fluorinated silicones allow users to deliver dose volumes as low as 8 μ l from standard dropper delivery systems. The human
25 ocular tear film is capable of accommodating volumes of only about 7 μ l. Thus, the ability to deliver small volumes to the eye results in little or no costly loss of drugs which are largely blinked away when the prior art 35 μ l - 50 μ l volume oil and water liquid carrier delivery
30 compositions are utilized to deliver pharmaceutical agents to the eye.

Accordingly, the present invention provides pharmaceutical compositions in the form of highly efficient, low dose volume, drop instillable mixtures of
35 a nonaqueous physiologically acceptable perfluorocarbon liquid carrier and at least one drug polymeric delivery vehicle incorporating a pharmaceutically effective amount

of a therapeutic or diagnostic compound. The low dose volumes are preferably less than 10 μ l. Preferably, the low dose volume, drop instillable mixtures are produced in the form of liquid suspensions of at least one polymeric drug delivery vehicle suspended in perfluorocarbon liquid carrier. Moreover, the preferred dose configuration of the pharmaceutical compositions of the present invention include a plurality of polymeric drug delivery vehicles in the form of microparticulates suspended in a perfluorocarbon liquid carrier.

Table I illustrates the dramatic distinction between the physical characteristic of water and that of two perfluorocarbons, PFD and PPP. The high density and remarkable low surface tension allows very small drop volumes to be formed with standard liquid droppers. By contrast, water is limited to forming drops in the range of 35 μ l - 50 μ l. Thus, the compositions of the present invention can be utilized to form advantageously small eye drops with standard droppers.

TABLE I

	<u>Water</u>	<u>PFD</u>	<u>PPP</u>
Molecular weight	18	462	624
25 Boiling point ($^{\circ}$ C)	100	142	215
Refractive index	1.333	1.31	—
Density @ 25 $^{\circ}$ C (gms/mL)	1.000	1.929	2.016
Kin. viscosity @ 25 $^{\circ}$ C (cst)	1.00	2.9	8.0
Heat of vaporization (g-cal/gm)	539.0	16.1	15.9
30 Specific heat @ 25 $^{\circ}$ C (g-cal/gm)	1.00	0.22	0.27
Surface tension @ 25 $^{\circ}$ C (dynes/cm)	72.0	19.3	21.6

Furthermore, as illustrated in Example 10, the bioavailability of pharmaceutical compounds utilized in the low volume, high efficiency pharmaceutical compositions of the present invention is substantially

higher than pharmaceutical compounds delivered in larger drop aqueous systems.

EXAMPLE 10

5 A comparison of the pharmacokinetic and pharmacologic characteristics of pilocarpine suspended in the perfluorocarbon versus pilocarpine in an aqueous solution was conducted on rabbits. This study involved delivering an
10 8 μ l dose of pilocarpine suspended in the perfluorocarbon to rabbits' eyes and a corresponding 35 μ l dose of the aqueous pilocarpine solution. The amount of pilocarpine actually retained by the eye following delivery
15 was quantitatively determined for both the perfluorocarbon based delivery and for the aqueous based delivery. It was observed that by delivering pilocarpine in the low volume perfluorocarbon suspension a 2.4 times higher
20 concentration of pilocarpine would remain in the eye as compared to the aqueous based 35 μ l dose of pilocarpine when the concentration is corrected for the total dose used. The study also showed that the pharmacological activity of
25 pilocarpine delivered in the perfluorocarbon suspension lasted 1 to 2 hours longer than the pharmacologic activity of pilocarpine delivered in the aqueous carrier. The results of this study illustrate the significantly greater
30 efficiency and bioavailability associated with pharmaceutical compounds delivered using the perfluorocarbon liquid carriers of the present invention.

35 Having thus described exemplary embodiments of the present invention, it should be noted by those skilled in the art that the disclosures herein are exemplary only and

that alternatives, adaptations and modifications may be made within the scope of the present invention. Accordingly, the present invention is not limited to the specific embodiments illustrated herein.

What is claimed is:

1. A pharmaceutical composition comprising:
 - 5 a nonaqueous fluorinated liquid carrier selected from the group consisting of perfluorocarbons and fluorinated silicones; and
 - at least one polymeric drug delivery vehicle suspended in said nonaqueous fluorinated liquid carrier,
 - 10 said drug delivery vehicle incorporating a pharmaceutically effect amount of a therapeutic or diagnostic compound.
2. The pharmaceutical composition of Claim 1
 - 15 wherein said perfluorocarbons are selected from the group consisting of perfluorocyclocarbons, nitrogen containing perfluorocyclocarbon derivatives, oxygen containing perfluorocyclocarbon derivatives, acyclic perfluorocarbons, nitrogen containing acyclic
 - 20 perfluorocarbon derivatives, and oxygen containing acyclic perfluorocarbon derivatives.
3. The pharmaceutical composition of Claim 2 wherein said perfluorocyclocarbons are selected from the
 - 25 group consisting of perfluorodecalin, perfluoroperhydrophenanthrene, perfluoromethylcyclohexane, perfluoro(1,3-dimethylcyclohexane), perfluorotrimethylcyclohexane, perfluoroisopropylcyclohexane, perfluoroendotetrahy-
 - 30 drodicyclopentadiene, perfluoro-1-methyl-4-isopropylcyclohexane, perfluoro-n-butylcyclohexane, perfluoro(decahydronaphthalene), perfluoro (decahydro-1-methylnaphthalene), perfluoro (decahydrodimethylnaphthalene), perfluoromethyladamantane,
 - 35 perfluorotrimethylbicyclo(3.3.1)nonane, perfluorodimethylbicyclo(3.3.1)nonane, and perfluoro-1-methyldecalin.

4. The pharmaceutical composition of Claim 2 wherein said nitrogen containing acyclic perfluorocarbon derivatives are selected from the group consisting of perfluorotributylamine and perfluorotriisopropylamine.

5

5. The pharmaceutical composition of Claim 2 wherein said oxygen containing perfluorocarbon derivatives are selected from the group consisting of perfluorotetrahydrofuran and perfluoroether.

10

6. The pharmaceutical composition of Claim 1 wherein said drug delivery vehicle comprises a polymer incorporating said therapeutic or diagnostic compound.

15

7. The pharmaceutical composition of Claim 1 wherein said drug delivery vehicle comprises a plurality of microparticulates, each of said microparticulates formed of a polymer matrix incorporating said therapeutic or diagnostic compound.

20

8. The pharmaceutical composition of Claim 7 wherein each of said microparticulates is sized from approximately 2 microns to 200 microns.

25

9. The pharmaceutical composition of Claim 1 wherein said drug delivery vehicle comprises a plurality of microcapsules, each of said microcapsules formed of an erodible polymer encapsulating said therapeutic or diagnostic compound.

30

10. The pharmaceutical composition of Claim 9 wherein each of said microcapsules is sized on the order of approximately 20 microns to 200 microns.

11. The pharmaceutical composition of Claim 6 wherein said polymer is a hydrolytically labile polymer selected from the group consisting of poly-(methylvinylether/maleic anhydride), polyfumaric
5 acid/sebacic acid, collagen, gelatin, polyvinyl alcohol, methylcelluloses, polyorthoesters, polyglycolic acid, polylactic acid, polyvinylpyrrolidone, polysebacic acid anhydride, polycarboxyphenoxypropane anhydride, polyterephthalic acid anhydride, and polyphosphazine.

10

12. The pharmaceutical composition of Claim 1 wherein said therapeutic or diagnostic compound is selected from the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics,
15 anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents.

20 13. The pharmaceutical composition of Claim 1 wherein said therapeutic or diagnostic compound is selected from the group consisting of epithelial growth factor, dipivalyl epinephrine hydrochloride, levo-bunolol hydrochloride, pilocarpine, sodium fluorescein,
25 tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, tobramycin, ciprofloxacin, norfloxacin, penicillin, erythromycin, cefazolin, ceftazadime, imipenem, idoxuridine, hydrocortisones, dexamethasone, dexamethasone 21 phosphate, fluocinolone,
30 medrysone, prednsolone acetate, fluormetholone, betamethasone, phenylephrine, eserine salicylate, carbachol, echothiophate iodide, demecarium bromide, cyclopentolate, homatropine, scopolamine, epinephrine, ibuprofen, aceclidine, teretinoin, and pirenoxine.

35

14. A pharmaceutical composition comprising:
a plurality of microparticulates suspended in a
perfluorocarbon liquid carrier, each of said
microparticulates sized from approximately 2 microns to
5 200 microns and incorporating a pharmaceutically effective
amount of a therapeutic or diagnostic compound.

15. The pharmaceutical composition of Claim 17
wherein said perfluorocarbon liquid carrier is selected
10 from the group consisting of perfluorocyclocarbons,
nitrogen containing perfluorocyclocarbon derivatives,
oxygen containing perfluorocyclocarbon derivatives,
acyclic perfluorocarbons, nitrogen containing acyclic
perfluorocarbon derivatives, and oxygen containing acyclic
15 perfluorocarbon derivatives.

16. The pharmaceutical composition of Claim 15
wherein said perfluorocyclocarbons are selected from the
group consisting of perfluorodecalin,
20 perfluoroperhydrophenanthrene, perfluoromethylcyclohexane,
perfluoro(1,3-dimethylcyclohexane),
perfluorotrimethylcyclohexane,
perfluoroisopropylcyclohexane, perfluoroendotetrahy-
drodicyclopentadiene,
25 perfluoro-1-methyl-4-isopropylcyclohexane, perfluoro-
n-butylcyclohexane, perfluoro(decahydronaphthalene),
perfluoro(decahydro-1-methylnaphthalene), and perfluoro
(decahydrodimethylnaphthalene), perfluoromethyladamantane,
perfluorotrimethylbicyclo(3.3.1.)nonane,
30 perfluorodimethylbicyclo(3.3.1)nonane, and
perfluoro-1-methyldecalin.

17. The pharmaceutical composition of Claim 15
wherein said nitrogen containing acyclic perfluorocarbon
35 derivatives are selected from the group consisting of
perfluorotributylamine and perfluorotriisopropylamine.

18. The pharmaceutical composition of Claim 15 wherein said oxygen containing derivatives are selected from the group consisting of perfluorotetrahydrofuran and perfluoroether.

5

19. The pharmaceutical composition of Claim 14 wherein said therapeutic or diagnostic compound is selected from the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics, 10 anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents.

15 20. The pharmaceutical composition of Claim 14 wherein said therapeutic or diagnostic compound is selected from the group consisting of epithelial growth factor, dipivalyl epinephrine hydrochloride, levo-bunolol hydrochloride, pilocarpine, sodium fluorescein, 20 tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, tobramycin, ciprofloxacin, norfloxacin, penicillin, erythromycin, cefazolin, ceftazadime, imipenem, idoxuridine, hydrocortisones, dexamethasone, dexamethasone 21 phosphate, fluocinolone, 25 medrysone, prednisolone acetate, fluormetholone, betamethasone, trimeinolone, phenylephrine, eserine salicylate, carbachol, phospholine iodide, demecarium bromide, cyclopentolate, homotropine, scopolamine, epinephrine, ibuprofen, aceclidine, teretinoin, and 30 pirenoxine.

21. A low volume, high bioavailability pharmaceutical composition comprising:

5 a low dose volume, drop instillable mixture of nonaqueous physiologically acceptable perfluorocarbon liquid carrier and at least one polymeric drug delivery vehicle incorporating a pharmaceutically effective amount of a therapeutic or diagnostic compound.

10 22. The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said low dose volume is less than 10 μ l.

15 23. The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said polymeric drug delivery vehicle comprises a plurality of microparticulates.

20 24. The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said low dose volume, drop instillable mixture is a suspension of a plurality of said drug polymeric delivery vehicles in said nonaqueous physiologically acceptable perfluorocarbon liquid carrier.

25 25. The low volume, high bioavailability pharmaceutical composition of claim 24 wherein said suspension includes a surfactant.

30 26. The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said nonaqueous perfluorocarbon liquid carrier is selected from the group consisting of perfluorocyclocarbons, nitrogen containing perfluorocyclocarbon derivatives, oxygen containing perfluorocyclocarbon derivatives, acyclic perfluorocarbons, nitrogen containing acyclic perfluorocarbon derivatives, and oxygen containing acyclic perfluorocarbon derivatives.

27. The low volume, high bioavailability pharmaceutical composition of claim 26 wherein said nonaqueous perfluorocarbon liquid carrier perfluorodecalin, perfluoroperhydrophenanthrene, 5 perfluoromethylcyclohexane, perfluoro(1,3-dimethylcyclohexane), perfluorotrimethylcyclohexane, perfluoroisopropylcyclohexane, perfluoroendotetrahyd-
drodicyclopentadiene, 10 perfluoro-1-methyl-4-isopropylcyclohexane, perfluoro-n-butylcyclohexane, perfluoro(decahydronaphthalene), perfluoro (decahydro-1-methylnaphthalene), perfluoro (decahydrodimethylnaphthalene), perfluoromethyladamantane, perfluorotrimethylbicyclo(3.3.1.)nonane, 15 perfluorodimethylbicyclo(3.3.1)nonane, and perfluoro-1-methyldecalin.

28. The low volume, high bioavailability pharmaceutical composition of claim 27 wherein said 20 nonaqueous perfluorocarbon liquid carrier is selected from the group consisting of perfluorodecalin and perfluoroperhydrophenanthrene.

29. The low volume, high bioavailability 25 pharmaceutical composition of claim 21 wherein said nitrogen containing acyclic perfluorocarbon derivatives are selected from the group consisting of perfluorotributylamine and perfluorotriisopropylamine.

30. The pharmaceutical composition of Claim 21 30 wherein said oxygen containing perfluorocarbon derivatives are selected from the group consisting of perfluorotetrahydrofuran and perfluoroether.

31. The pharmaceutical composition of Claim 21 wherein said polymer is as hydrolytically labile polymer selected from the group consisting of poly-(methylvinylether/maleic anhydride), polyfumaric
5 acid/sebacic acid, collagen, gelatin, polyvinyl alcohol, methylcelluloses, polyorthoesters, polyglycolic acid, polylactic acid, polyvinylpyrrolidone, polysebacic acid anhydride, polycarboxyphenoxypropane anhydride, polyterephthalic acid anhydride, and polyphosphazine.

10

32. The pharmaceutical composition of Claim 21 wherein said therapeutic or diagnostic compound is selected from the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics,
15 anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents.

20

33. The pharmaceutical composition of Claim 21 wherein said therapeutic or diagnostic compound is selected from the group consisting of epithelial growth factor, dipivalyl epinephrine hydrochloride, levo-bunolol hydrochloride, pilocarpine, sodium fluorescein,
25 tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, tobramycin, ciprofloxacin, norfloxacin, penicillin, erythromycin, cefazolin, ceftazadime, imipenem, idoxuridine, hydrocortisones, dexamethasone, dexamethasone 21 phosphate, fluocinolone,
30 medrysone, prednsolone acetate, fluormetholone, betamethasone, phenylephrine, eserine salicylate, carbachol, echothiophate iodide, demecarium bromide, cyclopentolate, homatropine, scopolamine, epinephrine, ibuprofen, aceclidine, teretinoin, and pirenoxine.

35

AMENDED CLAIMS

[received by the International Bureau on 2 September 1993 (02.09.93);
original claims 6,14-20 and 28 cancelled;
original claims 1-5, 7-13, 21,22,24,27,29-33 amended;
other claims unchanged (7 pages)]

1. (Amended) A drop instillable, low dose volume pharmaceutical composition with high bioavailability comprising:

a nonaqueous fluorinated liquid carrier selected
5 from the group consisting of perfluorocarbons and fluorinated silicones; and

at least one polymeric drug delivery vehicle suspended in said nonaqueous fluorinated liquid carrier, said drug delivery vehicle associated with a pharmaceu-
10 tically effective amount of at least one therapeutic or diagnostic compound.

2. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 1 wherein said non-aqueous fluorinated liquid carrier is a perfluorocarbon selected from the group consisting of perfluorocyclo-
5 carbons, nitrogen containing perfluorocyclocarbon derivatives, oxygen containing perfluorocyclocarbon derivatives, acyclic perfluorocarbons, nitrogen containing acyclic perfluorocarbon derivatives, and oxygen containing acyclic perfluorocarbon derivatives.

3. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 2 wherein said perfluorocarbon is a perfluorocyclocarbon selected from the group consisting of perfluorodecalin, perfluoroperhydro-
5 phenanthrene, perfluoromethylcyclohexane, perfluoro-(1,3-dimethylcyclohexane), perfluorotrimethylcyclohexane, perfluoroisopropylcyclohexane, perfluoroendotetrahydrodicyclopentadiene, perfluoro-1-methyl-4-isopropylcyclohexane, perfluoro-n-butylcyclohexane, perfluoro(decahydro-
10 naphthalene), perfluoro(decahydro-1-methylnaphthalene), perfluoro(decahydrodimethylnaphthalene), perfluoromethyladamantane, perfluorotrimethylbicyclo(3.3.1.)nonane,

perfluorodimethylbicyclo(3.3.1)nonane, and perfluoro-1-methyldecalin.

4. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 2 wherein said perfluorocarbon is a nitrogen containing acyclic perfluorocarbon derivative selected from the group consisting of
5 perfluorotributylamine and perfluorotriisopropylamine.

5. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 2 wherein said perfluorocarbon is an oxygen containing acyclic perfluorocarbon derivative selected from the group consisting of
5 perfluorotetrahydrofuran and perfluoroether.

6. Cancelled.

7. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 1 wherein said polymeric drug delivery vehicle comprises a plurality of microparticulates incorporating said therapeutic or
5 diagnostic compound.

8. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 7 wherein each of said microparticulates is sized from approximately 2 microns to approximately 200 microns.

9. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 1 wherein said polymeric drug delivery vehicle comprises a plurality of microcapsules, each of said microcapsules comprising an
5 erodible polymer encapsulating said therapeutic or diagnostic compound.

10. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 9 wherein each of said microcapsules is sized from approximately 20 microns to approximately 200 microns.

11. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 1 wherein said polymeric drug delivery vehicle comprises a hydrolytically labile polymer selected from the group consisting of poly-
5 (methylvinylether/maleic anhydride), polyfumaryl
acid/sebacic acid, collagen, gelatin, polyvinyl alcohol,
methylcelluloses, polyorthoesters, polyglycolic acid,
polylactic acid, polyvinylpyrrolidone, polysebacic acid
anhydride, polycarboxyphenoxyp propane anhydride,
10 polyterephthalic acid anhydride, and polyphosphazene.

12. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 1 wherein said therapeutic or diagnostic compound is selected from the group consisting of protein growth factors, oligopeptides,
5 antibacterials, antihistaminics, anti-inflammatories,
miotics, anticholinergics, mydriatics, antiglaucomals,
antiparasitics, antivirals, carbonic anhydrase inhibitors,
antifungals, anesthetics, diagnostic agents, and
immunosuppressive agents.

13. (Amended) The drop instillable, low dose volume pharmaceutical composition of Claim 1 wherein said therapeutic or diagnostic compound is selected from the group consisting of epithelial growth factor, dipivalyl epi-
5 nephrine hydrochloride, levo-bunolol hydrochloride, pilo-
carpine, sodium fluorescein, tetracycline, chlortetracy-
cline, bacitracin, neomycin, polymyxin, gramicidin, tobra-
mycin, ciprofloxacin, norfloxacin, penicillin, erythro-
mycin, cefazolin, ceftazadime, imipenem, idoxuridine,
10 hydrocortisones, dexamethasone, dexamethasone 21 phos-

phate, fluocinolone, medrysone, prednisolone acetate, fluormetholone, betamethasone, phenylephrine, eserine salicylate, carbachol, echothiophate iodide, demecarium bromide, cyclopentolate, homatropine, scopolamine, epinephrine, ibuprofen, aceclidine, teretinoin, and pirenoxine.

14. Cancelled.

15. Cancelled.

16. Cancelled.

17. Cancelled.

18. Cancelled.

19. Cancelled.

20. Cancelled.

21. (Amended) A low volume, high bioavailability pharmaceutical composition comprising:

a low dose volume, drop instillable mixture of a nonaqueous physiologically acceptable perfluorocarbon liquid carrier and at least one polymeric drug delivery vehicle associated with a pharmaceutically effective amount of at least one therapeutic or diagnostic compound.

22. (Amended) The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said low dose volume is between approximately 5 μ l and approximately 30 μ l.

23. The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said polymeric drug

delivery vehicle comprises a plurality of microparticulates.

24. (Amended) The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said low dose volume, drop instillable mixture is a suspension of a plurality of polymeric microparticulates incorporating
5 at least one therapeutic or diagnostic compound in said nonaqueous physiologically acceptable perfluorocarbon liquid carrier.

25. The low volume, high bioavailability pharmaceutical composition of claim 24 wherein said suspension includes a surfactant.

26. The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said nonaqueous perfluorocarbon liquid carrier is selected from the group consisting of perfluorocyclocarbons, nitrogen containing
5 perfluorocyclocarbon derivatives, oxygen containing perfluorocyclocarbon derivatives, acyclic perfluorocarbons, nitrogen containing acyclic perfluorocarbon derivatives, and oxygen containing acyclic perfluorocarbon derivatives.

27. (Amended) The low volume, high bioavailability pharmaceutical composition of claim 26 wherein said nonaqueous perfluorocarbon liquid carrier is a perfluorocyclocarbon selected from the group consisting of perfluorodecalin, perfluoro-perhydrophenanthrene, perfluoromethylcyclohexane, perfluoro(1,3-dimethylcyclohexane),
5 perfluorotrimethylcyclohexane, perfluoroisopropylcyclohexane, perfluoroendotetrahydrodicyclopentadiene, perfluoro-1-methyl-4-isopropylcyclohexane, perfluoro-
10 n-butylcyclohexane, perfluoro(decahydronaphthalene), perfluoro (decahydro-1-methylnaphthalene), perfluoro (decahydrodimethylnaphthalene), perfluoromethyladamantane,

perfluorotrimethylbicyclo(3.3.1.)nonane, perfluorodimethylbicyclo(3.3.1)nonane, and perfluoro-1-methyldecalin.

28. Cancelled.

29. (Amended) The low volume, high bioavailability pharmaceutical composition of claim 21 wherein said nonaqueous perfluorocarbon liquid carrier is a nitrogen containing acyclic perfluorocarbon derivative selected from the group consisting of perfluorotributylamine and perfluorotriisopropylamine.

30. (Amended) The low volume, high bioavailability pharmaceutical composition of Claim 21 wherein said nonaqueous perfluorocarbon liquid carrier is an oxygen containing perfluorocarbon derivative selected from the group consisting of perfluorotetrahydrofuran and perfluoroether.

31. (Amended) The low volume, high bioavailability pharmaceutical composition of Claim 21 wherein said polymeric drug delivery vehicle is a hydrolytically labile polymer selected from the group consisting of poly-(methylvinylether/maleic anhydride), polyfumalic acid/sebacic acid, collagen, gelatin, polyvinyl alcohol, methylcelluloses, polyorthoesters, polyglycolic acid, polylactic acid, polyvinylpyrrolidone, polysebacic acid anhydride, polycarboxyphenoxypropane anhydride, polyterephthalic acid anhydride, and polyphosphazine.

32. (Amended) The low volume, high bioavailability pharmaceutical composition of Claim 21 wherein said therapeutic or diagnostic compound is selected from the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics, anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals,

antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic agents and immunosuppressive agents.

33. (Amended) The low volume, high bioavailability pharmaceutical composition of Claim 21 wherein said therapeutic or diagnostic compound is selected from the group consisting of epithelial growth factor, dipivalyl
5 epinephrine hydrochloride, levo-bunolol hydrochloride, pilocarpine, sodium fluorescein, tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, tobramycin, ciprofloxacin, norfloxacin, penicillin, erythromycin, cefazolin, ceftazadime,
10 imipenem, idoxuridine, hydrocortisones, dexamethasone, dexamethasone 21 phosphate, fluocinolone, medrysone, prednisolone acetate, fluormetholone, betamethasone, phenylephrine, eserine salicylate, carbachol, echothiophate iodide, demecarium bromide, cyclopentolate,
15 homatropine, scopolamine, epinephrine, ibuprofen, aceclidine, teretinoin, and pirenoxine.

STATEMENT UNDER ARTICLE 19

To further define the present invention and to clarify the features which differentiate it from the references cited by the International Searching Authority, claims 1-5, 7-13, 21, 22, 24, and 27-33 have been amended. More specifically the amended claims are directed to nonaqueous pharmaceutical compositions which exhibit high bioavailability for very low dose volumes. These fluorinated liquid compositions of drug associated microparticulates have a superior shelf life and are particularly useful for small volume drop installation administration.

In contrast, cited European patent application 0 322 249 discloses water based purified collagen combined with liquid perfluorocarbons for use in wound healing. Contrary to the nonaqueous low dose volume fluorinated compositions of the present invention, the collagen mixture is formulated as an aqueous perfluorocarbon emulsion for large volume topical application. The formation of a water based emulsion precludes the small volume drop installation of the disclosed collagen

formulations. Moreover, unlike the stable compositions of the present invention, the presence of water in these emulsions can degrade biologically active molecules, severely limiting their stability and reducing their bioavailability.

Similarly, cited PCT application 8 400 686 also discloses the use of aqueous perfluorocarbon emulsions to sensitize hypoxic tumors, but for adjunct therapies utilizing intravenous or systemic administration of relatively large volumes of the aqueous emulsion. To preclude agglomeration of the sensitizer *in vivo*, this reference further teaches the necessity of mixing the perfluorocarbon with an aqueous dispersion medium. This is in direct contrast to the pharmaceutical compositions of the present invention which use undiluted fluorinated compounds to reduce the dose volume, enhance the stability and increase the bioavailability of the associated active compounds.

Finally, cited PCT application 9 118 613 discloses self-emulsifying glasses containing oleaginous material which, on contact with aqueous solutions, form stable emulsions. This is in sharp contrast to the claimed compositions which are formulated as flowing, low dose volume drop instillable mixtures in a fluorinated liquid. The emulsions disclosed in this reference would prevent the formation of the small drops of the present invention and reduce the overall stability and the bioavailability of the emulsion components.

Accordingly, the claimed invention as reflected in these amended claims is both novel and inventive with respect to these references.

1/2
IN VITRO RELEASE OF SODIUM FLUORESCIN
FROM GANTREZ MICROSPHERES AFTER
BEING STORED IN PFC AT 23°C

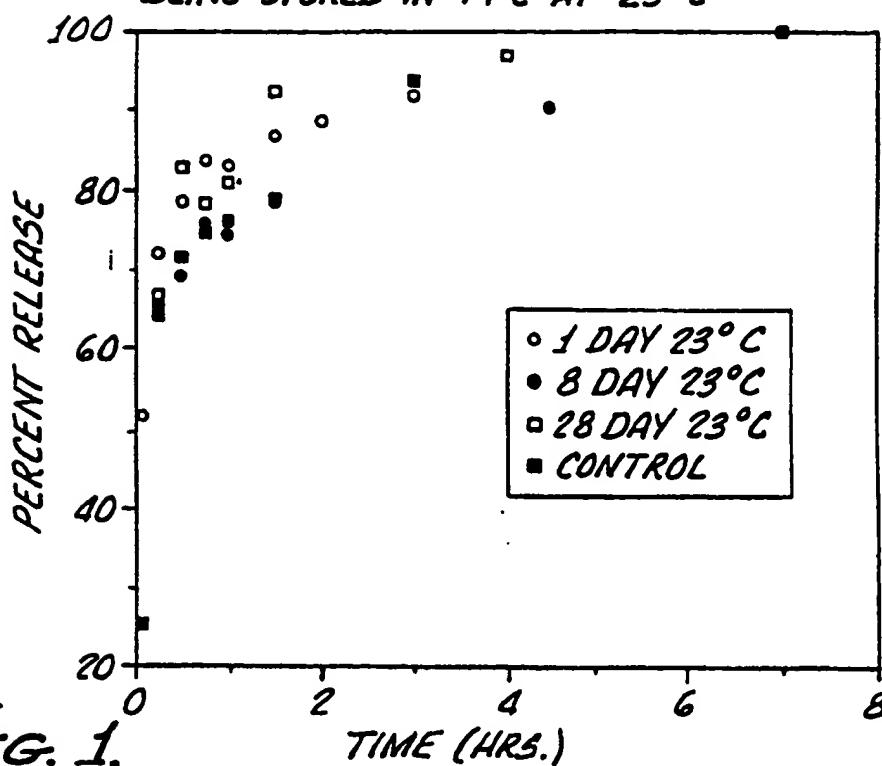


FIG. 1.

IN VITRO RELEASE OF SODIUM FLUORESCIN
FROM GANTREZ MICROSPHERES AFTER
BEING STORED IN PFC AT 45°C

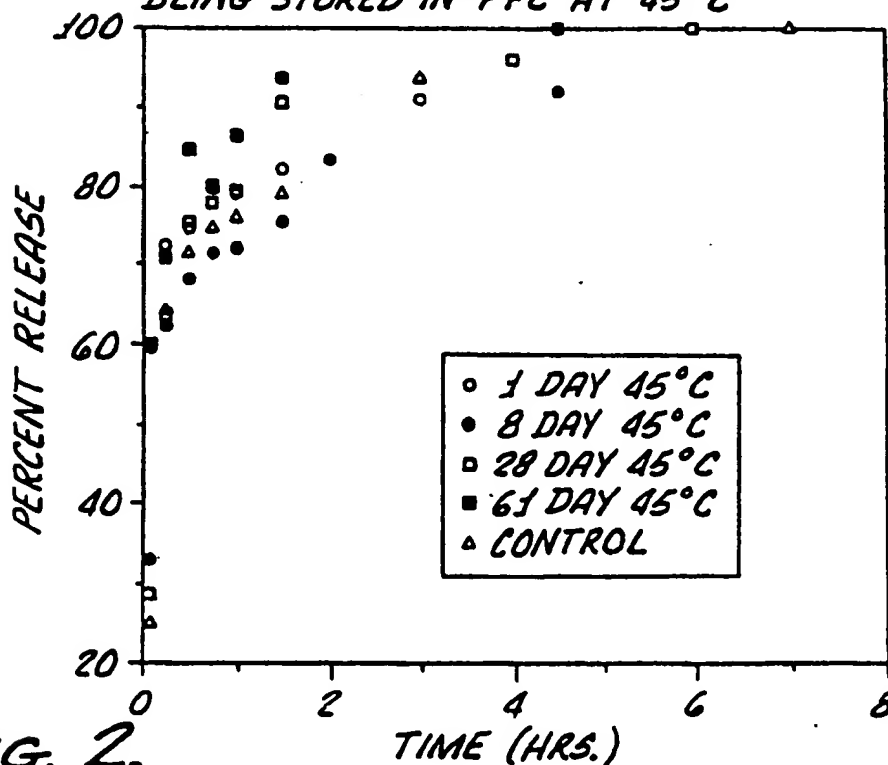


FIG. 2.

2/2

DPE MICROSPHERES STORED IN
PERFLUORODECALIN AT 37°C
(5% SUSPENSION)

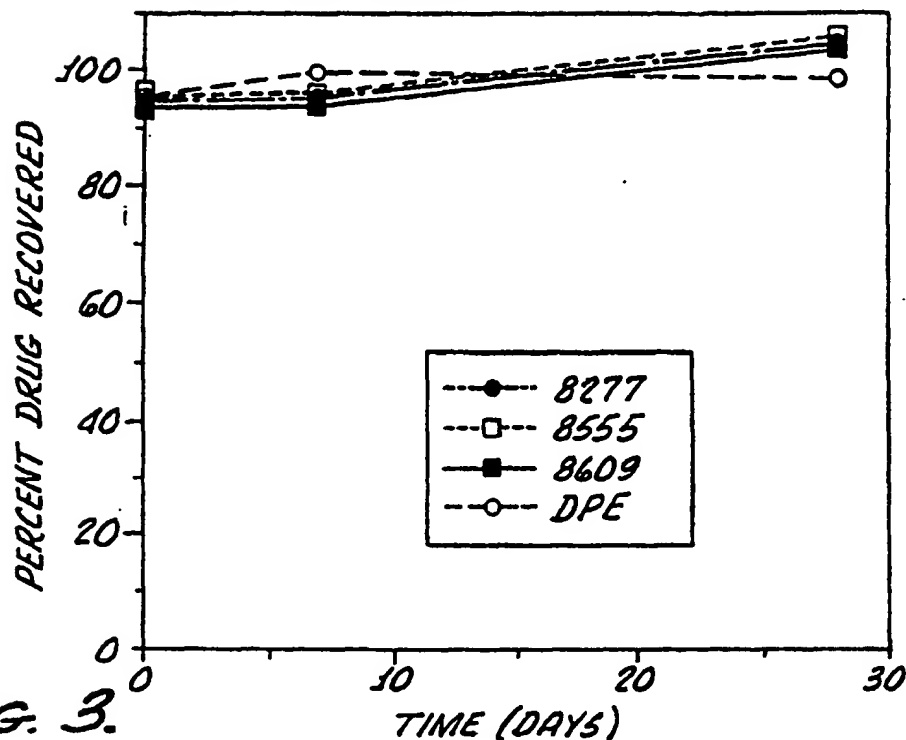


FIG. 3.

DPE MICROSPHERES STORED IN
PERFLUORODECALIN AT AMBIENT
TEMPERATURE (5% SUSPENSION)

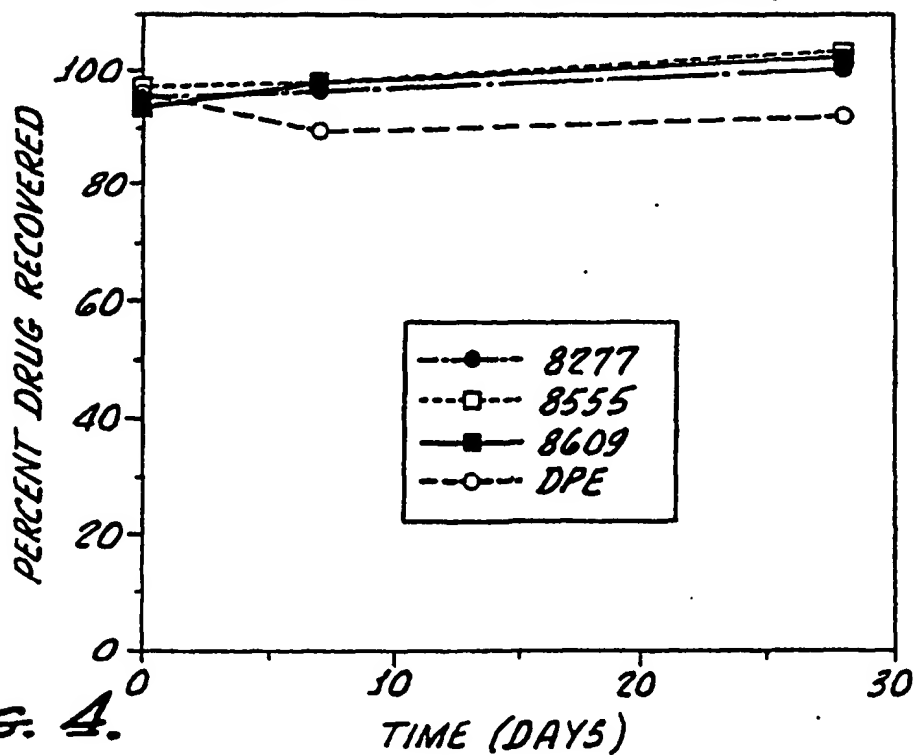


FIG. 4.

INTERNATIONAL SEARCH REPORT

PCT/US 93/02500

International Application No.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K9/10; A61K9/00; A61K9/16		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	EP,A,0 322 249 (YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUS.) 28 June 1989 see claims 1-3,5 see page 4, line 1 - line 31	1-4,6,7, 11,12
X	WO,A,8 400 686 (SUN TECH INC.) 1 March 1984 see claims 1,2,9 see page 8, line 31 - page 9, line 18 see page 13, line 18 - page 14, line 14 see page 17, line 34 - page 18, line 8 -/--	1-3,5,6, 11
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
25 JUNE 1993	JUN 27 1993	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	VENTURA AMAT A.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	WO,A,9 118 613 (RESEARCH CORPORATION TECHNOLOGIES INC.) 12 December 1991 see claims 1,6,14-17 see page 41, line 23 - page 42, line 6 see page 44, line 20 - page 45, line 4 -----	1-3,6,11
P,X	WO,A,9 205 770 (ALLERGAN INC.) 16 April 1992 see the whole document -----	1-33

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9302500
SA 72216

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

25/06/93

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